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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEESER, ERICH A	
ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
03/31/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nyuspatactions@ladas.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,711	XU ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11 and 19-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to Applicant's submission dated February 5, 2010. Claims 1-7, 9-11, and 19-27 are pending and under examination.

Claim Rejections - 35 USC § 112

Examine previously rejected claims 19-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; treat a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion using an effective amount of a compound corresponding of formula (I) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Applicant argues that it is not proper for the Office to use a state of the art reference to show what is not known in the art and cites six references in support of enablement of the instant invention. Because these references tend to show enablement with regards to renal disorders, diabetes, cardio-cerebrovascular diseases, and tumors; Examiner withdraws this rejection with regards to claims 21, 23-24, and 26, but maintains the rejection with regards to claims 19-20, 22, and 25.

Claim Rejections - 35 USC § 102

Examiner previously rejected claims 1-2, 4, 6-7, and 9-11 under 35 USC 102(b) as being anticipated by Chinese Patent No. CN 1207392A, which teaches coumarin and coumarin-amide derivatives, and includes the instant compounds. Specifically, the compounds of the abstract and pages 1-2 of the reference anticipate the aforementioned claims where instant R^3 is $CONHR_9$ and R_9 is phenyl either unsubstituted or substituted with hydroxyl, alkoxy, carboxyl, nitro, halogen or SO_3H, and instant R^4-R^8 are all hydrogen.

Based on Applicant's arguments of record, Examiner withdraws this rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for "prophylaxis" of a tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The only established prophylactics are vaccines not the coumarin compounds such as present here. In addition, it is presumed that "prophylaxis" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no

evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, prophylaxis of a tumor requires identifying those patients who will acquire the tumor before metastases occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) Applicant intends the invention to act as a prophylaxis against tumors. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical oncology medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become cancerous before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in oncology with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of oncological diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo*

Nordisk, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent tumors generally. That is, the skill is so low that no compound effective generally against tumors has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by formula (I).

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making a "prodrug" of the claimed compounds. The claims contain subject matter that is not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to make and use the invention.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The nature of the invention

Fused heterocyclic coumarin-amide derivatives, including "further comprising an ester or prodrug thereof."

The state of the prior art:

The state of the prodrug art is summarized by Wolff, Manfred E., *Burger's Medicinal Chemistry and Drug Discovery*, Fifth Ed., Vol. 1: Principles and Practice, John Wiley & Sons, 1995, 975. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker, Gilbert S. et al., *Modem Pharmaceutics*, Marcel Dekker, New York, 1996, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

The predictability or lack thereof in the art:

It is well-established that "the scope of enablement varies inversely to the degree of unpredictability of the factors involved", "and physiological activity is generally considered to be an unpredictable factor." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. First, the prodrug must itself be biologically inactive. Second, the prodrug must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

The amount of direction or guidance present:

The amount of guidance or direction refers to that information in the application that teaches exactly how to make or use the invention. The specification contains no working examples of a prodrug of a compound of the formula (I). Thus, undue experimentation will be required by one skilled in the art to make the prodrugs of the claimed invention.

The presence or absence of working examples:

The specification contains no working examples of a prodrug of a compound of the formula (I). Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

The breadth of the claims:

The breadth of the claims includes all of the hundreds of compounds of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by this term. This term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed prodrugs of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the prodrugs of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The quantity of experimentation needed

Substantial and undue experimentation would be needed to practice Applicant's invention because he did not sufficiently detail how to make and use a "prodrug" of the instant invention.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to make and use the instantly claimed invention.

Claims 1-7, 9-11, and 19-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making hydrates of the claimed invention. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, insofar as they embrace hydrates are not enabled. The numerous examples presented all failed to produce a hydrate. The evidence of the specification is thus clear: These compounds do not possess the property of forming hydrates; there is no evidence that such compounds even exist. Thus, this is a circumstance where the "specification is evidence of its own inadequacy". *In re Rainer* , 377 F.2d 1006, 1012, 153 USPQ 802, 807. These cannot be simply willed into existence. As was stated in *Morton Int'l Inc. v. Cardinal Chem. Co.*, 28 USPQ2d 1190: "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance

appears to be true here: there is no evidence that hydrates of these compounds actually exist; if they did, they would have formed. Hence, Applicant must show that hydrates can be made, or limit the claims accordingly.

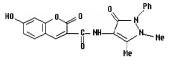
With regard to *Morton Int'l Inc. v. Cardinal Chem. Co.*, 28 USPQ2d 1190, the Court held lack of enablement because the disclosed procedures in the specification did not even produce the claimed compounds. That is exactly the case here as well. One skilled in the art knows that hydrates are prepared by exposing the compound to water (e.g. by preparing in the presence of water) and then isolating the solid. If the compound inherently forms hydrates, then one will get a hydrate; if not, one will not. That is, some compounds form hydrates; some do not. These compounds, judging by the evidence of the specification, are in the latter category. The specification teaches no methods for overcoming this deficiency, i.e. to force a compound, which does not naturally form one, to form a hydrate. The specification does not even seem to be aware of the problem. The remarks do not state how to do this, nor does Examiner know of any such technique.

Claim Rejections - 35 USC § 102

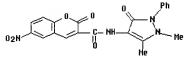
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 10-11 and 27 are rejected under 35 USC 102(b) as being anticipated by El-Kerdawy, et al., *Application of the Knoevenagel Condensation to 4-acetamidophenazone Derivatives*, Indian J. of Chemistry, Section B: Organic Chem. Including Medicinal Chem., 26B(12), 1189-91 (1987). El-Kerdawy, et al. teaches 4-acetamidophenazone derivatives, which include instant compounds. Specifically, the compounds N-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-7-hydroxy-2-oxo-2H-1-benzopyran-3-carboxamide with the following structure:

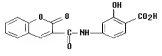


of the reference anticipates the aforementioned claims where R_3 is the first option, R_4, R_5, R_6, and R_8 are hydrogen, and R_7 is hydroxyl.



of the reference anticipates the aforementioned claims where R_3 is the first option, R_4, R_5, R_7, and R_8 are hydrogen, and R_6 is nitro. These compounds are found in Scheme 1 at the bottom of page 1190 of the reference.

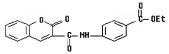
Claims 1, 4, 10-11 and 27 are rejected under 35 USC 102(e) as being anticipated by Levy, et al., U.S. Patent Publication No. 2003/0229065. Levy, et al. teaches transcription factor modulating compounds, which include instant compounds. Specifically, the compound



of the

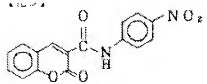
reference anticipates the aforementioned claims where R_3 is $CONHR_9$, R_9 is phenyl, R'_2, R'_3, R'_6, R_4, R_5, R_6, R_7, and R_8 are hydrogen, R'_4 is carboxylic acid, and R'_5 is hydroxy. This compound is called ADJ and is found in Table 5 on page 226 of the reference.

Claims 1-2 and 4 are rejected under 35 USC 102(b) as being anticipated by Bylov, et al., *Synthesis and Anti-inflammatory Activity of N-substituted 2-oxo-2H-1-benzopyran-3-carboxyamides and Their 2-iminoanalogues*, Eur. J. Med. Chem. 34, 997-1001 (1999). Bylov, et al. teaches N-substituted 2-oxo-2H-1-benzopyran-3-carboxyamides and their 2-iminoanalogues useful as anti-inflammatory agent, which include instant compounds. Specifically, the compound



of the reference anticipates the aforementioned claims where R_3 is $CONHR_9$, R_9 is phenyl, R'_2, R'_3, R'_5, R'_6, R_4, R_5, R_6, R_7, and R_8 are all hydrogen, and R'_4 is CO_2Et. This compound is 4b and is found in Table 1 on page 998 of the reference.

Claims 1-2, 4, 10-11 and 27 are rejected under 35 USC 102(b) as being anticipated by Ogiso, et al., JP 06145164. Ogiso, et al. teaches benzopyranone and benzothiopyranone derivatives as UV-absorbents, which include instant compounds. Specifically, the compound:



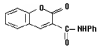
(III)

of the reference anticipates the aforementioned claims

where R_3 is $CONHR_9$, R_9 is phenyl, R'_2, R'_3, R'_5, R'_6, R_4, R_5, R_6, R_7, and R_8 are all hydrogen, and R'_4 is nitro. This compound is of formula (III) and is found in the first column on page 2 of the reference.

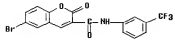
Also, the

compound:



of the reference anticipates the aforementioned claims where R_3 is $CONHR_9$, R_9 is unsubstituted phenyl, R'_2, R'_3, R'_5, R'_6, R'_4, R_4, R_5, R_6, R_7, and R_8 are all hydrogen. This compound is the fourth of five and is found in the table on page 14 of the reference.

Claims 1-2, 4, 10-11 and 27 are rejected under 35 USC 102(b) as being anticipated by Reusser, et al., WO 89/07939. Reusser, et al. teaches coumarins to inhibit reverse transcriptase in humans for treatment of human immunodeficiency virus infection, which include instant compounds. Specifically, the compound



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reference anticipates the aforementioned claims where R_3 is $CONHR_9$, R_9 is phenyl, R'_2, R'_4, R'_5, R'_6, R_4, R_5, R_7, and R_8 are all hydrogen, R'_3 is CF_3, and R_6 is halogen (bromine). This compound is found in on page 8 of the reference.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103 that form the basis for the rejections under this section made in this Office action:

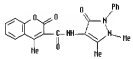
1. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1-3, 10-11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over El-Kerdawy, et al., *Application of the Knoevenagel Condensation to 4-acetamidophenazone Derivatives*, Indian J. of Chemistry, Section B: Organic Chem. Including Medicinal Chem., 26B(12), 1189-91 (1987).

Determining the scope and contents of the prior art.

El-Kerdawy, et al. teaches 4-acetamidophenazone derivatives, very similar to the instant compounds. Specifically, the compound N-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-4-methyl-2-oxo-2H-1-benzopyran-3-carboxamide with the following structure:



renders the instant claims obvious when R_3 is the first option, R_7, R_5, R_6, and R_8 are hydrogen, and R_4 is methyl. This compound is found in Scheme 1 at the bottom of page 1190 of the reference.

Ascertaining the difference between the prior art and the claims at issue.

The claims at issue differ from the prior art because the claims at issue do not provide for methyl at position R_4, only hydrogen. However, many of the other R groups allow for alkyl, which includes methyl, such as R_5, R_6, and R_8. It is well-established that position isomers are *prima facie* structurally obvious even in the absence of a teaching to modify. The isomer is expected to be made by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This situation has arisen many times in the courts. *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullyot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 247, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154; and *In re Mayne*, 41 USPQ2d 1451, 1454-1455 (the court took notice of the extreme similarity between the amino acids Leucine and isoleucine: "In fact, Leu is an isomer of Ile -- an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains…of Leu and Ile have the same number of hydrogen and carbon atoms…The structure of Leu and Ile alone suggest their functional equivalency").

"Position isomerism is a fact of close structural similarity". *In re Mehta*, 146 USPQ 284, 287. "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". *In re Jones*, 21 USPQ2d 1942, 1943. Position isomers are the basic form of close "structural isomers." "[A] novel useful chemical compound which is homologous or isomeric

with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." *In re Schechter and LaForge*, 98 USPQ 144, 150. "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds … a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para)." *In re Deuel* 34 USPQ2d 1210, 1214. See also MPEP 2144.09, second paragraph.

In addition, it is well established that the substitution of methyl for hydrogen, or vice versa, on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Wood*, 199 USPQ 137 (CCPA 1978) and *In re Lohr*, 137 USPQ 548, 549 (CCPA 1963). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity.

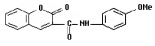
Resolving the level of skill in the art.

It would have required little more than routine modification of the synthesis of compounds of the reference by one having ordinary skill in this art at the time the invention was made to prepare a compound within the scope of the compounds instantly claimed as applicants have done with the above-cited journal article before them. The variants show the interchangeability of the overlapping substituents.

3. Claims 1-4, 10-11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ukhov, et al., *Synthesis and Antimicrobial Activity of 2-Iminocoumarin-3-carboxylic acid amides*, Pharmaceutical Chemistry Journal, Vol. 35, No. 7 (2001).

Determining the scope and contents of the prior art.

Ukhov, et al. teaches 2-iminocoumarin-3-carboxylic acid amides, very similar to the instant compounds. Specifically, the compound with the following structure:



renders the instant claims obvious when R_3 is $CONHR_9$, R'_2, R'_3, R'_5, R'_6, R_7, R_5, R_6, and R_8 are hydrogen, R_9 is phenyl, and R'_4 is methoxy. This compound is called III and is found on page 364, first column, of the reference.

Ascertaining the difference between the prior art and the claims at issue.

Here, the claims allow for hydroxy, but not methoxy at position R'_4. It is well established that the substitution of methyl for hydrogen, or vice versa, on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Wood*, 199 USPQ 137 (CCPA 1978) and *In re Lohr*, 137 USPQ 548, 549 (CCPA 1963). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity.

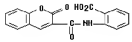
Resolving the level of skill in the art.

It would have required little more than routine modification of the synthesis of compounds of the reference by one having ordinary skill in this art at the time the invention was made to prepare a compound within the scope of the compounds instantly claimed as applicants have done with the above-cited journal article before them. The variants show the interchangeability of the overlapping substituents.

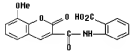
4. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bylov, et al., *Synthesis and Anti-inflammatory Activity of N-substituted 2-oxo-2H-1-benzopyran-3-carboxyamides and Their 2-iminoanalogues*, Eur. J. Med. Chem. 34, 997-1001 (1999).

Determining the scope and contents of the prior art.

Bylov, et al. teaches N-substituted 2-oxo-2H-1-benzopyran-3-carboxyamides and their 2-iminoanalogues useful as anti-inflammatory agents, very similar to the instant compounds. Specifically, the compound with the following structure:

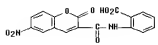


renders the instant claims obvious when R_3 is $CONHR_9$, R'_2, R'_3, R'_4, R'_5, R_7, R_5, R_6, and R_8 are hydrogen, and R'_6 is carboxy. This compound is 4c found in Table 1 on page 998 of the reference. Also, the compound with the following structure:



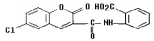
renders the instant claims obvious when R_3 is $CONHR_9$, R'_2, R'_3, R'_4, R'_5, R_7, R_5, and R_6 are hydrogen, R_8 is methoxy, and R'_6 is carboxy. This compound is 4e found in Table 1 on page 998 of the reference.

Further, the compound with the following structure:



renders the instant claims obvious when R_3 is $CONHR_9$, R'_2, R'_3, R'_4, R'_5, R_7, R_5, and R_8 are all hydrogen, R_6 is nitro, and R'_6 is carboxy. This compound is 4f found in Table 1 on page 998 of the reference.

the compound with the following structure:



renders the instant claims obvious when R_3 is $CONHR_9$, R'_2, R'_3, R'_4, R'_5, R_7, R_5, and R_8 are all hydrogen, R_6 is halogen, and R'_6 is carboxy. This compound is 4g found in Table 1 on page 998 of the reference.

Ascertaining the difference between the prior art and the claims at issue.

The claims at issue differ from the prior art because the claims at issue do not provide for carboxy at position R'_6. However, many of the other R groups allow for carboxy, such as R'_2, R'_3, and R'_4. It is well-established that position isomers are *prima facie* structurally obvious even in the absence of a teaching to modify. The isomer is expected to be made by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This situation has arisen many times in the courts. *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullyot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 247, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154; and *In re Mayne*, 41 USPQ2d 1451, 1454-1455 (the court took notice of the extreme similarity between the amino acids Leucine and isoleucine: "In fact, Leu is an isomer of Ile -- an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains…of Leu

and Ile have the same number of hydrogen and carbon atoms…The structure of Leu and Ile alone suggest their functional equivalency").

"Position isomerism is a fact of close structural similarity". *In re Mehta*, 146 USPQ 284, 287. "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". *In re Jones*, 21 USPQ2d 1942, 1943. Position isomers are the basic form of close "structural isomers." "[A] novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." *In re Schechter and LaForge*, 98 USPQ 144, 150. "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds … a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para)." *In re Deuel* 34 USPQ2d 1210, 1214. See also MPEP 2144.09, second paragraph.

Resolving the level of skill in the art.

It would have required little more than routine modification of the synthesis of compounds of the reference by one having ordinary skill in this art at the time the invention was made to prepare a compound within the scope of the compounds instantly claimed as applicants have done with the above-cited journal article before them. The variants show the interchangeability of the overlapping substituents.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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